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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,254	09/10/2004	Jose M. Carballido Herrera	PD/4-32483A	6363

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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,254	CARBALLIDO HERRERA ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *1-4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/10/04, 8/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-4 in the reply filed on November 16, 2005 is acknowledged. The election of the species of IL-4 is further acknowledged.

2. Claims 5-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Priority

Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP03/04793, filed 5/7/03, which claims priority to United Kingdom application No. 0210535.1, filed 5/8/02.

Information Disclosure Statement

Applicant's Information Disclosure Statements (IDS) filed 9/10/04 and 8/9/05 have been received and entered into the application.

The US Patent Document 715,332 (Cite No. AA on Applicant's IDS of 8/9/05) has not been considered by the Examiner. The document was not accessible via a search of the US Patent databases using the EAST program since the document's publication date is over 100 years ago. If Applicant believes the document to be pertinent to the patentability of the invention and wishes it to be considered by the Examiner, it is requested that a copy of the document be supplied.

Document DE29803626 (Cite No. AN on Applicant's IDS of 8/9/05) and document DE4120139 (Cite No. AN on Applicant's IDS of 9/10/04) have not been considered by the Examiner as they are German language documents.

Only the abstract of document EP0408542 (Cite No. AR on the IDS of 8/9/05) has been considered because only the abstract has been supplied as an English translation.

Only the abstracts of Documents AS (Geysen) and AT (Matsuda et al.) on the IDS of 8/9/05 have been considered by the Examiner since only the abstracts were provided.

Specification

3. The abstract of the disclosure is objected to because it is not in narrative form and includes legal phraseology. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

4. The specification is objected to because it the arrangement is not in accordance with the guidelines below and does not include required section headings.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without

underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

5. The disclosure is objected to because of the following informalities:

The word "cytokines" is misspelled at p. 14, line 6

The name of the cell line appears as "#98016T**o**" at p. 14, line 9, in Figure 3, and at p. 15, lines 5 and 30, etc. but as "#98016T**0**" at p. 13, line 28 and at p. 4, line 16.

The word "empty" is misspelled at p. 14, line 11.

The word "Celsius" is misspelled at p. 14, line 21.

6. The use of trademarks ("VICTOR2™", "TWEEN™", FACSCAN™", "CELLQUEST™", "MAXISORP™", "SPECTRAMAX™", "SOFTMAX™", "DELFIA™") has been noted in this application (see p. 17, lines 8, 15, 18-19, 26, and 34; p. 16, lines 6-7, 11, 14, and 21-22; and Figure 2). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Objections

7. Claims 1-4 are objected to because of the following informalities:

8. Claim 1 appears to require a colon at the end of the preamble in line 2.

9. Claim 1 recites in part (f) the step of providing a matrix comprising pins that are coated with a coating mixture comprising at least two different recognition molecules, "from each of which it is known that it will bind at a specific binding site to one of the analytes". The phrase is grammatically awkward and it is unclear what the subjects "each of which" and "it" are referring to. Similarly, in part (h) the claim recites "2 different detection molecules, from which detection molecules it is known that each will bind to a specific site of one of the recognition complexes".

10. Claim 1 recites "at least 2 analytes", "at least 2 different recognition molecules", and "at least 2 different detection molecules" in parts (a), (f) and (h), respectively. It is suggested that the numeral "2" should be spelled out as "two" in the claims.

11. Claim 1 recites "adding **a** candidate compound" in step (d). This would seem to refer back to the candidate compound recited in step (c). If this is Applicant's intention, it is suggested that step (d) refer to "said candidate compound" or "the candidate compound".

12. Part (g) of claim 1 is a run-on sentence (at "each recognition complex").

13. Claims 2-4 recite "human IL-4, IL-10 and IFN-γ". As written, it seems that the adjective "human" is intended to modify only IL-4, while it would seem that it is intended to modify IL-10 and IFN-γ as well.

14. Claims 3-4 recite groups consisting of "antibodies to human IL-4, IL-10 and IFN-γ", which suggests that the group members are (1) antibodies to human IL-4, (2) IL-10, and (3) IFN-γ". It would seem that the claims intend to refer to (1) antibodies to human IL-4, (2) antibodies to human IL-10, and (3) antibodies to human IFN-γ.

15. Claim 4 recites "the said detection molecule". It would seem that either "the detection molecule" or "said detection molecule" would be sufficient.

16. Claim 4 is a run-on sentence (at "said detection molecule").

Appropriate correction is required.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. Claim 1 recites a method for identifying an agent that "has an influence on" the amount of an analyte expressed by a cell. The term "has an influence on" is indefinite, as the term could refer to an increase, a decrease, etc. The claim does not clearly specify what type(s) of "influence" would be encompassed by the term.

20. Claim 1 recites "at least 2 analytes" in part (a) and further recites providing means for stimulation of a cell to express "**such analytes**" in part (b). The phrase "such" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

21. Claim 1 recites adding a candidate compound "shortly" after contacting in part (d). The term "shortly" is a relative term which renders the claim indefinite. The term "shortly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear what time periods would be encompassed by "shortly after".

22. Claim 1 recites "optionally disrupting cells" in part (e). This would seem to refer to the cell that is recited in the preamble and in parts (a), (b), and (d); however, these portions of the claim refer to a cell (singular) and not to "cells".

23. Claim 1 recites "optionally disrupting cells" in part (e). It is unclear whether this step is actually performed in the method. Step (g) recites contacting the pins of the matrix of (f) with the medium obtained in (d), but there is no further reference back to the cells of part (e) in the claim. In addition, step (g) recites contacting the "medium obtained in (d)" with the matrix. This would seem to indicate that the medium still comprises cells at this point, since the medium of (d) refers back to the medium recited in step (a), which recites that the medium comprises a *cell.* However,

the cells may be disrupted in step (e). Such a "disruption" would seem to include disruption by cell lysis. In this case, the medium would no longer comprise cells *per se*, but cell lysate.

24. Claim 1 recites "disrupting" cells in part (e). The term is vague and indefinite and is not defined in the specification. It is unclear in what sense the cells are "disrupted" or what cellular processes or structures would be affected by disruption.

25. The term "sufficient period of time" in claim 1, parts (g) and (i), is a relative term that renders the claim indefinite. The term "sufficient period of time" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of what time periods would be sufficient according to the invention.

26. The term "specific binding site" in part (f) is indefinite. The term is not defined in the specification. It is unclear what is meant by a "specific binding site".

27. Claim 1 refers to the binding of "one single analyte to its specific recognition molecule". It is unclear whether "one single analyte" refers to a single molecule of an analyte or to one type of analyte, i.e. to one of the "at least 2 analytes" referred to in part (a).

28. Claim 1 recites in step (k) comparing the amount of detection complex formed in "the absence" and in "the presence of" a candidate compound. There is insufficient antecedent basis for these limitations in the claims. Step (d) recites adding a candidate compound **or** adding no candidate compound, but does not recite that both of these are performed in the method. Therefore, it is unclear how the absence and presence of the candidate compound are compared in step (k) since step (d) does not require both scenarios.

29. The preamble of claim 1 recites a method for identifying an "agent". Step (l) also refers to "an agent". However, steps (c), (d), and (k) refer to a "candidate compound". It is unclear how an "agent" is identified by the method as the process steps refer to a "candidate compound". If "agent" and the "candidate compound" are referring to the same chemical entity, it is suggested that a consistent term be used throughout the claim.

30. Claims 2 and 4 recite "said analyte" in the singular form. There is insufficient antecedent basis for this term since claim 1 recites "at least 2 analytes". It is unclear which of the at least two analytes is being referred to.

31. Similarly, claims 3-4 refer to "said recognition molecule", "the recognition molecule", and "said detection molecule" in the singular form. There is insufficient antecedent basis for this term since claim 1 recites "at least 2 different recognition molecules" and "at least 2 different detection molecules". It is unclear which of the at least two molecules are being referred to.

32. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a correlation step describing how the results of the detection relate back to the method objective recited in the preamble (identification of an agent that influences the amount of analyte expressed by a cell). Step (l) recites that an agent is chosen which influences the amount of a *detection complex*, but there is no correlation step in which an agent is identified which influences the amount of *analyte expressed by a cell*. Alternatively, active method steps may be recited that clearly relate back to the preamble.

Claim Rejections - 35 USC § 103

33. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

34. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cocks et al. (*Nature* (1995) **376**:260-263, Applicant's Information Disclosure statement of 9/10/04) in view of in view of Fish et al. and as evidenced by Chretien et al. ("Development of polyclonal and monoclonal antibodies for immunoassay and neutralization of human interleukin-4" *J Immunol Methods* (1989) Feb 8;117(1):67-81).

Cocks et al. teach a method for identifying an agent that has an influence on the amount of an analyte (cytokine) expressed by a cell (T cell clone), comprising providing a medium comprising the cell, which has the ability to express at least two analytes upon stimulation (see in particular p. 260-261, especially the paragraph bridging the pages and Figure 3 and legend). Cocks et al. further teach providing means for stimulation of the cell to express cytokines

(specific antigen) and a candidate compound (anti-SLAM mAb A12 or control antibody) see legends to Figures 2-3). The method of Cocks comprises contacting the cell-containing medium with the means of stimulation in order to obtain stimulated T-cell clones, adding the candidate compounds, harvesting the cells, and assaying for cytokine expression by ELISA. The amount of analyte produced (in this case, IL-4 and IFN-γ; see Figure 3) is compared for the cells with and without candidate compound (anti-SLAM mAb A12 and control antibody) and choosing an agent (anti-SLAM mAb A12) that has an influence on the amount of analyte produced (Figures 3, compare the open, shaded, and filled columns). In particular, Cocks et al. note that IFN-γ production was strongly enhanced by addition of anti-SLAM mAb A12 (see the paragraph bridging p. 260-261).

As noted above, Cocks et al. teach that the cytokines were measured by ELISA. However, Cocks et al. do not specifically teach the procedural details of this ELISA assay, but refer to a prior publication (Chretien et al.) in which the assay is described (see Cocks et al. at the legend to Figure 3, the last three lines). Therefore, the Chretien et al. reference is being relied on as evidence that the following procedures would necessarily be performed in the method of Cocks et al.

The cytokine ELISA of Chretien et al. detects human IL-4 via a two-site sandwich ELISA (p. 70, "Immunoenzymetric (two-site sandwich) assay" and p. 76-77, "Human IL-4 immunoenzymetric assay"). The assay comprises the steps of providing a matrix (PVC plates) on which are a coated recognition molecule that binds to the analyte (anti-IL-4 antibody). The matrix is contacted with cell supernatants (Tables I-II) for a period of time sufficient to allow formation of recognition complexes, and providing a detection antibody (11B4 antibody directly

labeled with horseradish peroxidase or indirectly conjugated; see p. 77, first paragraph). The detection antibody binds to IL-4 without interfering with the binding of IL-4 to the coated anti-IL-4 antibody since the IL-4 is able to be successfully detected following washing of the matrix (see Fig. 7). It binds to a different epitope (site) than that recognized by the coated anti-IL-4 antibody since the assay described is a *two-site* assay (see p. 76, "Human IL-4 Immunoenzymetric assay"). It would also be immediately apparent to one skilled in the art that in such a sandwich ELISA kit the Detection Antibody would bind to the recognition complex without interfering with the binding of the analyte to the Coating antibody; see also the instant specification at p. 6, lines 21-29, which discloses that such sandwich ELISA formats are appropriate systems for performing the method of the invention. The detection antibody is contacted with the matrix to form a detection complex (sandwich) between the detection antibody and the IL-4/coated anti-IL-4 antibody complex, and the amount of detection complex formed on the matrix is detected using a colorimetric substrate by measuring the optical density of the samples (p. 69-70).

Cocks et al. fail to specifically teach a matrix comprising **pins** that are coated with a **coating mixture** of at least two different recognition molecules. In the method of Cocks et al. (as evidenced above by Chretien et al.) the matrix is an ELISA plate upon which a single recognition molecule is coated; the multiple cytokines that are detected in Cocks et al. are detected multiple (parallel) sandwich ELISA assays for the individual cytokines.

Fish et al. (as discussed above) teach a solid phase immunoassay system for assaying at least one analyte (the abstract and column 1, line 64 to column 2, line 3), in which the matrix ("solid support") comprises a plurality of pins ("tabs" **3**) (column 2, lines 53-68; column 6, lines

40-62; Figures 1-2). The tabs anticipate the instant limitation of "pins" as Fish et al. teach that they can assume a variety of configurations and may be round, tubular, rod, cylindrical, etc. (column 6, lines 41-46). Fish et al. teach that each of the tabs has at least one receptor for an analyte, and may have a *plurality of receptors for different analytes*, (column 2, lines 63-68). Fish et al. teach that this type of solid phase is desirable because it enables a plurality of unknown analytes to be screened in a single assay (column 1, line 52 to column 2, line 10). It also enables one to simultaneously assay a plurality of samples without risk of cross-contamination (see also column 2, lines 26-30).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the pin-comprising matrix of Fish et al. in the method of Cocks et al. because Fish et al. teach that such a matrix enables a plurality of analytes to be screened in a single assay, which would be applicable to the method of Cocks et al. in which a plurality of analytes are measured.

One would have reasonable success in using the pin-containing matrix of Fish et al. instead of the ELISA plate in the method of Cocks et al. because Fish et al. teach that the recognition molecules or receptors that are immobilized on the pins may be antibodies (column 6, lines 63-68), and that the solid phase can be used in sandwich immunoassays (column 9, lines 4-7), which is the assay employed in the method of Cocks et al. (as evidenced by Chretien et al.).

36. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. ("Effect of an Orally Active Th1/Th2 Balance Modulator, M50367, on IgE Production, Eosinophilia, and Airway Hyperresponsiveness in Mice" (*The Journal of Immunology* (1999) **162**:7470-7479) in view of Fish et al. and as evidenced by Pierce (Endogen® Searchlight ™ Mouse IL-2 ELISA

MiniKit product information sheet) and Crowther ("ELISA: Theory and Practice" *Methods in Molecular Biology* Vol. 42 (1995) Humana Press, Inc., Totowa, NJ, pages 39-43).

Kato et al. teach a method for identifying an agent that has an influence on the amount of cytokines expressed by mouse splenocyte cells, comprising providing a medium comprising a cell with the ability to express at least 2 analytes (the cytokines IFN-γ, IL-2, IL-4, and IL-5) upon stimulation ("sensitization"), and providing a means for stimulation of the cells to express the cytokines (DNP-Ascaris or ConA) (see Kato et al. at p. 7474, the "Materials" section at "Ag, mitogen, and Abs", and right column, "Mice sensitized with DNP-Ascaris" and "Direct effect on splenocyte Th1/Th2 cytokine production"; and p. 7474, Table 1, in particular comparing the lines "Normal splenocytes" and "sensitized splenocytes"). Kato et al. further teach providing a candidate compound (the drugs M50354, prenisolone, or cyclosporine A) and contacting the medium with the DNP-Ascaris or ConA and with the candidate compound (see p. 7471, "Direct effect on splenocyte Th1/Th2 production", the first paragraph). Kato et al. teach that the medium and cells were "cultured in the presence of...DNP-Ascaris or...ConA **with**...drugs" (emphasis added). This would seem to indicate that the candidate compound (drug) was added simultaneously with the means of stimulation, although this is not entirely clear. In any event, this teaching anticipates the claim limitation of adding a candidate compound "before, simultaneously or shortly after" contacting with the means of stimulation.

Kato et al. further teach that cytokine levels were analyzed by sandwich ELISA kits (see also p. 7471, right column, first paragraph). The Pierce reference is relied upon for providing well-known procedural details that are not explicitly provided in Kato et al. but which would be necessarily performed in the use of the sandwich ELISA kits described by Kato et al. Pierce et al.

evidence that the sandwich ELISA kits used by Kato et al. comprise a matrix (plate) with a coating of a recognition molecule (Anti-IL-2 Coating Antibody) that will bind to the analyte (IL-2 in this case). The Pierce reference also provides evidence that use of the ELISA kit in Kato et al. would necessarily comprise the step of contacting the matrix with the cell culture supernate for a sufficient period of time (overnight) to allow for the formation of recognition complexes between IL-2 and the IL-2 Coating antibody (see "Sample Incubation" in particular). Use of the kit would also comprise the step of providing a detection molecule (Biotinylated Anti-IL-2 Detection Antibody). It would also be immediately apparent to one skilled in the art that in such a sandwich ELISA kit the Detection Antibody would bind to the recognition complex without interfering with the binding of the analyte to the Coating antibody; see also the instant specification at p. 6, lines 21-29, which discloses that such sandwich ELISA formats are appropriate systems for performing the method of the invention. The Pierce reference also evidences that use of the sandwich ELISA kit by Kato et al. would necessarily involve contacting the Detection Antibody with the matrix for a sufficient period of time (1 hour) to allow formation of detection complexes (see "Detection Antibody Incubation") as well as determining the amount of detection complex formed on the matrix (see "Streptavidin-HRP Incubation" and "Substrate and Stop Solution").

Kato et al. further teach comparing the amount of cytokine detected by the sandwich ELISA kit formed in both the absence and in the presence of candidate compounds (see Table 1, comparing the "Vehicle" data with the candidate compound data (M50354, Cyclosporin A, and Prenisolone). Kato et al. further teaching choosing an agent which has an influence on the amount of cytokine detected in the sandwich ELISA kit (see p. 7473-7474, "Th1/Th2 balance in

DNP-Ascaris-sensitized mice" and "Direct effect on splenocyte Th1/Th2 cytokine production"). For example, Kato et al. note that the compound M50367 caused increased production of IFN-γ by splenocytes and caused reduced production of IL-4 and IL-5 in a dose-dependent manner (p. 7473, left column).

Kato et al. fail to specifically teach a matrix comprising **pins** that are coated with a **coating mixture** of at least two different recognition molecules. In Kato et al., the matrix is an ELISA plate upon which a single recognition molecule is coated; the multiple cytokines are detected in multiple sandwich ELISA assays for the individual cytokines (p. 7471, right column, first paragraph).

Fish et al. (as discussed above) teach a solid phase immunoassay system for assaying at least one analyte (the abstract and column 1, line 64 to column 2, line 3), in which the matrix ("solid support") comprises a plurality of pins ("tabs" **3**) (column 2, lines 53-68; column 6, lines 40-62; Figures 1-2). The tabs anticipate the instant limitation of "pins" as Fish et al. teach that they can assume a variety of configurations and may be round, tubular, rod, cylindrical, etc. (column 6, lines 41-46). Fish et al. teach that each of the tabs has at least one receptor for an analyte, and may have a *plurality of receptors for different analytes*, (column 2, lines 63-68). Fish et al. teach that this type of solid phase is desirable because it enables a plurality of unknown analytes to be screened in a single assay (column 1, line 52 to column 2, line 10). It also enables one to simultaneously assay a plurality of samples without risk of cross-contamination (see also column 2, lines 26-30).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the pin-comprising matrix of Fish et al. in the method of Kato et al. because Fish et al. teach that such a matrix enables a plurality of analytes to be screened in a single assay.

One would have reasonable success in using the pin-containing matrix of Fish et al. instead of the ELISA plate in the method of Kato et al. because Fish et al. teach that the recognition molecules or receptors that are immobilized on the pins may be antibodies (column 6, lines 63-68), and that the solid phase can be used in sandwich immunoassays (column 9, lines 4-7), which is the assay employed in the method of Kato et al.

Conclusion

37. No claims are allowed.

38. Regarding Documents CA 2,228,821, EP 0241140, (Applicant's Information Disclosure statement of 9/10/04), which were cited on the International Search Report, the documents have been considered by the Examiner and are considered to be pertinent but the prior art made of record above was perceived to be more relevant to the claims.

39. Carbadillo et al. (Applicant's Information Disclosure statement of 9/10/04), which were cited on the International Search Report, is of relevance and contains teachings similar to those found in Cocks et al. above.

40. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

41. Sanchez-Martinez (US 2004/0043398 A1, which claims priority to provisional application No. 60/372,527, filed April 15, 2002) teaches a multipin platform device for

performing screening assays in which the pins are coated with recognition molecules (ligands) (see Figure 1 and [0012]-[0013] in particular).

42. Okamoto et al. ("Development of a dual color enzyme-linked immunospot assay for simultaneous detection of murine T helper type 1- and T helper type 2-cells" (1998) *Immunopharmacology* **39**:107-116) is cited for its teaching of an assay for expression of the two cytokines IL-2 and IL-4 using a **mixture of antibodies** coated on a microtiter plate (see section 2.5 and Figures 1-2 in particular). However, Okamoto et al. fails to specifically teach identification of an agent that influences expression of the cytokines.

43. Nguyen et al. (US 2002/0137097 A1) is also cited for its teaching of multiplex immunoassays, e.g. sandwich immunoassays, that can be used to detect analytes such as IL-4 or other cytokines, wherein solid supports are coated with mixtures of capture reagents. Nguyen et al. teach that an advantage of the multiplex format is that multiple analytes can be detected in a single assay, such as in a well ([0004], [0007], [0022], [0025], [0028], [0038]).

44. Enomoto et al. ("High Throughput Screening for Human Interferon-g Production Inhibitor Using Homogenous Time-Resolved Fluorescence" *Journal of Biomolecular Screening* (2000) **5**:263-268) is cited for its teaching of a cell-based immunoassay to screen for inhibitors of IFN-γ cytokine production (see Fig. 1 in particular). Enomoto et al. teach a sandwich format in which recognition and detection antibodies to IFN-γ are employed to detect IFN-γ expression in response to IL-12 stimulation. However, Enomoto et al. fail to teach a matrix comprising pins; in Enomoto et al. both of the antibodies are added in solution and are not adsorbed to a solid phase.

45. Artursson et al. ("Inferferon-a Production and Tissue Localization of Interferon-a/b Producing Cells after Intradermal Administration of Aujeszky's Disease Virus-Infected Cells in

Pigs" (1995) *Scand. J. Immunol.* **41**:121-129), Goulet et al. (US Patent No. 6,329,380 B1), and Giuliani et al. (US Patent No. 6,518,316 B1) are cited for their teachings of assays for cytokine production by dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA). See Artursson et al. at p. 123, Goulet et al. at column 29, line 49 to column 50, line 9), and Guiliani et al. at column 21, line 58 to column 22, line 67).

46. Ebner et al. (US 6,486,301) teaches DELFIA assays for the analytes Erk-1 and Erk-2 (column 82, line 50 to column 83, line 32).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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